Please amend the application as follows:

In the Specification

Replace the paragraph at page 4, lines 20 through 27 with the following paragraph:

A1

The invention also relates to an isolated cell that produces an antibody or antigen-binding fragment of the present invention, including those which bind to mammalian GPR-9-6 and inhibit the binding of a ligand to the receptor. In a particular embodiment, the isolated cell is murine hybridoma 3C3 (also referred to as murine hybridoma LS129-3C3-E3-1) deposited under ATCC Accession No. HB-12653. In another particular embodiment, the isolated cell is murine hybridoma GPR96-1 (also referred to as murine hybridoma LS272 GPR96 1-5) deposited under ATCC Accession No. PTA-1470.

Replace the paragraph at page 6, lines 3 through 10 with the following paragraph:

A2

The invention also relates to an isolated cell that produces an antibody or antigen-binding fragment of the present invention, including those which bind to mammalian TECK and inhibit the binding of TECK to a receptor. In a particular embodiment, the isolated cell is murine hybridoma 11.3.1 (also referred to as murine hybridoma LS250 11.3.1) deposited under ATCC Accession No. PTA-1469. In another particular embodiment, the isolated cell is murine hybridoma 16.3.1 (also referred to as murine hybridoma LS250 16.3.1) deposited under ATCC Accession No. PTA-1468.

Replace the paragraph at page 8, lines 9 through 13 with the following paragraph:

A3

IN5 DY

Figures 2A-2B illustrate the specific binding of mAb 3C3 to GPR-9-6 transfectants. In Figure 2A, GPR-9-6/L1.2 transfectants were stained with mAb 3C3 (solid profile), anti-CCR6 antibody (·····) or with a murine IgG2b mAb (----) (n=2). In Figure 2B, CCR6/L1.2 transfectants

INS D1

A3 cont'd

were stained with mAb 3C3 (·····), anti-CCR6 antibody (solid profile) or with a murine IgG2b mAb (----) (n=2).

Replace the paragraph at page 18, lines 7 through 16 with the following paragraph:

Other suitable methods of producing or isolating antibodies of the requisite specificity (e.g., human antibodies or antigen-binding fragments) can be used, including, for example, methods which select recombinant antibody from a library (e.g., a phage display library), or

A4

which rely upon immunization of transgenic animals (e.g., mice) capable of producing a repertoire of human antibodies. Transgenic animals capable of producing a repertoire of human antibodies (e.g., XenoMouse (Abgenix, Fremont, CA) can be produced using suitable methods (see e.g., Jakobovits *et al., Proc. Natl. Acad. Sci. USA, 90*: 2551-2555 (1993); Jakobovits *et al., Nature, 362*: 255-258 (1993); Lonberg *et al.*, U.S. Patent No. 5,545,806; Surani *et al.*, U.S. Patent No. 5,545,807; Lonberg *et al.*, WO97/13852).

Replace the paragraph bridging pages 18 and 19 with the following paragraph:

In a particular embodiment, the antibody or antigen-binding fragment can inhibit the binding of a mammalian (e.g., human) TECK to mammalian (e.g., human) GPR-9-6 and/or one

A5

or more functions mediated by GPR-9-6 in response to TECK binding. In a particularly preferred embodiment, the antibody or antigen-binding fragment can inhibit the binding of TECK to GPR-9-6 and, thereby inhibit TECK-induced chemotaxis.

Replace the paragraph bridging pages 19 and 20 with the following paragraph:

As described herein, an antibody designated "mAb 3C3" that binds human GPR-9-6 has

A6

been produced. mAb 3C3 can be produced by murine hybridoma 3C3, also referred to as murine hybridoma LS129-3C3-E3-1 which was deposited on March 4, 1999, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75

Sidney Street, Cambridge, MA 01239), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110, U.S.A., under Accession No. HB-12653. In another embodiment, the anti-GPR-9-6 antibody of the invention is mAb 3C3 or an antigen-binding fragment thereof. In another embodiment, the binding of the antibody or antigen-binding fragment to mammalian (e.g., human) GPR-9-6 can be inhibited by mAb 3C3. Such inhibition can be the result of competition for the same or similar epitope, steric interference or due to a change in the conformation of GPR-9-6 that is induced upon antibody binding to the receptor. In still another embodiment, the antibody or antigen-binding fragment of the invention has the same or similar epitopic specificity as mAb 3C3. Antibodies with an epitopic specificity which is the same as or similar to that of mAb 3C3 can be identified by a variety of suitable methods. For example, an antibody with the same or similar epitopic specificity as mAb 3C3 can be identified based upon the ability to compete with mAb 3C3 for binding to mammalian GPR-9-6. In another example, the binding of mAb 3C3 and the binding of an antibody with the same or similar epitopic specificity to mammalian GPR-9-6 can be inhibited by a single peptide (e.g., natural peptide, synthetic peptide). The peptide can comprise nine to about fifty amino acids. Preferably, the peptide comprises nine to about twenty-six amino acids. In still another example, an antibody with the same or similar epitopic specificity as mAb 3C3 can be identified using chimeric receptors (see e.g., Rucker *et al.*, *Cell* 87:437-446 (1996)).

Replace the paragraph at page 20, lines 12 through 27 with the following paragraph:

As described herein, an antibody designated "mAb GPR96-1" that binds human GPR-9-6 has been produced. mAb GPR96-1 can be produced by murine hybridoma GPR96-1, also referred to as murine hybridoma LS272 GPR96 1-5, which was deposited on March 9, 2000, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 01239), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110, U.S.A., under Accession No. PTA-1470. In another embodiment, the anti-GPR-9-6 antibody of the invention is mAb GPR96-1 or an antigen-binding fragment thereof. In another embodiment, the binding of the

antibody or antigen-binding fragment to mammalian (e.g., human) GPR-9-6 can be inhibited by mAb GPR96-1. Such inhibition can be the result of competition for the same or similar epitope, steric interference or due to a change in the conformation of GPR-9-6 that is induced upon antibody binding to the receptor. In still another embodiment, the antibody or antigen-binding fragment of the invention has the same or similar epitopic specificity as mAb GPR96-1. Antibodies with an epitopic specificity which is the same as or similar to that of mAb GPR96-1 can be identified by a variety of suitable methods, such as those described herein.

A7

Replace the paragraph bridging pages 23 and 24 with the following paragraph:

As described herein, an antibody designated "mAb 11.3.1" that binds human TECK has been produced. mAb 11.3.1 can be produced by murine hybridoma 11.3.1, also referred to as murine hybridoma LS250 11.3.1, which was deposited on March 9, 2000, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 01239), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110, U.S.A., under Accession No. PTA-1469. In another embodiment, the anti-TECK antibody of the invention is mAb 11.3.1 or an antigen-binding fragment thereof. In another embodiment, the binding of the antibody or antigen-binding fragment to mammalian (e.g., human) TECK can be inhibited by mAb 11.3.1. Such inhibition can be the result of competition for the same or similar epitope, steric interference or due to a change in the conformation of TECK that is induced upon antibody binding to the receptor. In still another embodiment, the antibody or antigen-binding fragment of the invention has the same or similar epitopic specificity as mAb 11.3.1. Antibodies with an epitopic specificity which is the same as or similar to that of mAb 11.3.1 can be identified by a variety of suitable methods. For example, an antibody with the same or similar epitopic specificity as mAb 11.3.1 can be identified based upon the ability to compete with mAb 11.3.1 for binding to mammalian TECK. In another example, the binding of mAb 11.3.1 and the binding of an antibody with the same or similar epitopic specificity to mammalian TECK can be inhibited by a single peptide (e.g., natural peptide, synthetic peptide). The peptide can comprise

A8

nine to about fifty amino acids. Preferably, the peptide comprises nine to about twenty-six amino acids. In still another example, an antibody with the same or similar epitopic specificity as mAb 11.3.1 can be identified using chimeric receptors (see e.g., Rucker *et al., Cell 87*:437-446 (1996)).

Replace the paragraph bridging pages 24 and 25 with the following paragraph:

As described herein, an antibody designated "mAb 16.3.1" that binds human TECK has been produced. mAb 16.3.1 can be produced by murine hybridoma 16.3.1, also referred to as murine hybridoma LS250 16.3.1, which was deposited on March 9, 2000, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 01239), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110, U.S.A., under Accession No. PTA-1468. In another embodiment, the anti-TECK antibody of the invention is mAb 16.3.1 or an antigen-binding fragment thereof. In another embodiment, the binding of the antibody or antigen-binding fragment to mammalian (e.g., human) TECK can be inhibited by mAb 16.3.1. Such inhibition can be the result of competition for the same or similar epitope, steric interference or due to a change in the conformation of TECK that is induced upon antibody binding. In still another embodiment, the antibody or antigen-binding fragment of the invention has the same or similar epitopic specificity as mAb 16.3.1. Antibodies with an epitopic specificity which is the same as or similar to that of mAb 16.3.1 can be identified by a variety of suitable methods, such as those described herein.

Replace the paragraph bridging pages 30 and 31 with the following paragraph:

In one embodiment, a functional variant of mammalian GPR-9-6 (e.g., a ligand binding variant) shares at least about 80% amino acid sequence similarity with said mammalian GPR-9-6, preferably at least about 90% amino acid sequence similarity, and more preferably at least about 95% amino acid sequence similarity with said mammalian GPR-9-6. In another

embodiment, a functional fusion protein comprises a first moiety which shares at least about 85% sequence similarity with a mammalian GPR-9-6, preferably at least about 90% sequence similarity, and more preferably at least about 95% sequence similarity with a mammalian GPR-9-6 (e.g., a human GPR9-6 (e.g., SEQ ID NO:2)). In another embodiment, a functional mammalian GPR-9-6 protein or functional variant of a mammalian GPR-9-6 protein shares at least about 80% amino acid sequence similarity, preferably at least about 90% amino acid sequence similarity, and more preferably at least about 95% amino acid sequence similarity with a naturally occurring human GPR-9-6 (e.g., SEQ ID NO:2). Amino acid sequence similarity can be determined using a suitable sequence alignment algorithm, such as the LASERGENE system (sequence assembly and alignment software; DNASTAR, Inc., Madison, WI), using the Clustal method with the PAM 250 residue weight table, a gap penalty of 10, a gap length penalty of 10 and default parameters (pairwise alignment parameters: ktuple = 1, gap penalty = 3, window = 4 and diagonals saved = 5). In another embodiment, a functional variant is encoded by a nucleic acid sequence which is different from the naturally-occurring nucleic acid sequence, but which, due to the degeneracy of the genetic code, encodes mammalian GPR-9-6 or a portion thereof.

#10 cont'd

Replace the paragraph bridging pages 33 and 34 with the following paragraph:

In one embodiment, a functional variant of mammalian TECK (e.g., a ligand binding variant) shares at least about 80% amino acid sequence similarity with said mammalian TECK, preferably at least about 90% amino acid sequence similarity, and more preferably at least about 95% amino acid sequence similarity with said mammalian TECK (e.g., SEQ ID NO:9, SEQ ID NO:11). In another embodiment, a functional fusion protein comprises a first moiety which shares at least about 85% sequence similarity with a mammalian TECK, preferably at least about 90% sequence similarity, and more preferably at least about 95% sequence similarity with a mammalian TECK (e.g., a human TECK (e.g., SEQ ID NO:9, SEQ ID NO:11)). In another embodiment, a functional mammalian TECK protein or functional variant of a mammalian TECK protein shares at least about 80% amino acid sequence similarity, preferably at least about 90% amino acid sequence similarity, and more preferably at least about 95% amino acid

#11

sequence similarity with a naturally occurring human TECK (e.g., SEQ ID NO:9, SEQ ID NO:11). Amino acid sequence similarity can be determined using a suitable sequence alignment algorithm, such as the LASERGENE system (sequence assembly and alignment software; DNASTAR, Inc., Madison, WI), using the Clustal method with the PAM 250 residue weight table, a gap penalty of 10, a gap length penalty of 10 and default parameters (pairwise alignment parameters: ktuple = 1, gap penalty = 3, window = 4 and diagonals saved = 5). In another embodiment, a functional variant is encoded by a nucleic acid sequence which is different from the naturally-occurring nucleic acid sequence, but which, due to the degeneracy of the genetic code, encodes mammalian TECK or a portion thereof.

A11

Replace the paragraph at page 34, lines 7 through 9 with the following paragraph:

A12

The invention also relates to naturally occurring variants of mammalian GPR-9-6 and mammalian TECK (e.g., splice variants, allelic variants) and to nucleic acids encoding the variants (e.g., SEQ ID NO:10, SEQ ID NO:11).

Replace the paragraph at page 34, lines 10 through 24 with the following paragraph:

A13

A composition comprising a mammalian GPR-9-6 or functional variant thereof can be used in a binding assay to detect and/or identify agents that can bind to the receptor or to detect and/or identify agents that can bind to TECK. Compositions suitable for use in a binding assay include, for example, cells which naturally express a mammalian GPR-9-6 or functional variant thereof (e.g., thymocytes, GPR-9-6^{+} CLA^{-ve} $\alpha 4\beta 7^{hi}$ CD4^{+} memory lymphocytes, cell lines (e.g., MOLT-4 (ATCC Accession No. CRL-1582), MOLT-13 (M. Brenner, Brigham and Women's Hospital, Boston, MA), intraepithelial lymphocytes (IEL), lamina propria lymphocytes (LPL)) and recombinant cells comprising an exogenous nucleic acid sequence which encodes a mammalian GPR-9-6 or functional variant thereof. Compositions suitable for use in a binding assay also include, membrane preparations which comprise a mammalian GPR-9-6 or functional variant thereof. Such membrane preparations can contain natural (e.g., plasma membrane) or

A13 cont'd synthetic membranes. Preferably, the membrane preparation is a membrane fraction of a cell that expresses a mammalian GPR-9-6 or a functional variant thereof.

Replace the paragraph at page 40, lines 12 through 24 with the following paragraph:

An agent which binds to a mammalian GPR-9-6 can also be assessed by monitoring cellular responses induced by active receptor, using suitable cells which express a mammalian GPR-9-6 or a functional variant thereof. For instance, exocytosis (e.g., degranulation of cells leading to release of one or more enzymes or other granule components, such as esterases (e.g., A14 serine esterases), perforin, and/or granzymes), inflammatory mediator release (such as release of bioactive lipids such as leukotrienes (e.g., leukotriene C_4)), and respiratory burst, can be monitored by methods known in the art or other suitable methods (see e.g., Taub, D.D. *et al., J. Immunol., 155:* 3877-3888 (1995), regarding assays for release of granule-derived serine esterases; Loetscher *et al., J. Immunol., 156*: 322-327 (1996), regarding assays for enzyme and granzyme release; Rot, A. *et al., J. Exp. Med., 176*: 1489-1495 (1992) regarding respiratory burst; Bischoff, S.C. *et al., Eur. J. Immunol., 23*: 761-767 (1993) and Baggiolini, M. and C.A. Dahinden, *Immunology Today, 15*: 127-133 (1994)).

Replace the paragraph at page 43, lines 6 through 22 with the following paragraph:

In vivo models of inflammation are available which can be used to assess the efficacy of antibodies and antigen-binding fragments of the invention as well as agents identified by the A15 methods described herein as *in vivo* therapeutics. For example, leukocyte infiltration upon intradermal injection of a chemokine and an antibody or antigen-binding fragment thereof reactive with mammalian GPR-9-6 into a suitable animal, such as rabbit, mouse, rat, guinea pig or primate (e.g., rhesus macaque) can be monitored (see e.g., Van Damme, J. *et al., J. Exp. Med., 176:* 59-65 (1992); Zachariae, C.O.C. *et al., J. Exp. Med. 171:* 2177-2182 (1990); Jose, P.J. *et al., J. Exp. Med. 179:* 881-887 (1994)). In one embodiment, skin biopsies are assessed histologically for infiltration of leukocytes (e.g., GPR-9-6$^+$ T cells). In another embodiment,

labeled cells (e.g., stably transfected cells expressing a mammalian GPR-9-6, labeled with ^{111}In for example) capable of chemotaxis and extravasation are administered to the animal. For example, an antibody or agent to be assessed which binds a mammalian GPR-9-6 can be administered, either before, simultaneously with or after a GPR-9-6 ligand or agonist (e.g., TECK) is administered to the test animal. A decrease of the extent of infiltration in the presence of antibody or agent as compared with the extent of infiltration in the absence of said antibody or agent is indicative of inhibition.

A15 amd

Replace the paragraph at page 69, lines 7 through 20 with the following paragraph:

Several different adhesion molecules are involved in trafficking of lymphocyte subsets to distinct physiologic location, such as peripheral lymph node (Gallatin, W.M., *et al., Nature, 304*:30-34 (1983)), Peyer's Patches (Hamman, A., *et al., J. Immunol., 152*:3282-3292 (1994); Andrew, D.P., *et al., Eur. J. Immunol., 26*:897-905 (1996)) and inflammatory sites (Frenette, P.S., *et al., Cell, 84*:563-574 (1996); Tietz, W.Y., *et al., J. Immunol., 161(2)*:963-970 (1998); Picker, L.J., *et al., J. Immunol., 145*:3247-3255 (1990)). It is thought that specific chemokine receptors expressed on these lymphocyte subsets may interact with chemokines expressed in the areas mediating leukocyte activation, arrest, and transendothelial migration. Thus, CD4 subsets defined by the expression of certain adhesion molecules, may also express known, orphan or as yet undiscovered chemokine receptors that are important for trafficking of the lymphocytes into these sites. The work described herein relates to one such chemokine receptor that may be involved in the selective trafficking memory CD4 and CD8 lymphocyte subsets to mucosal sites.

A16

Replace the paragraph bridging pages 71 and 72 with the following paragraph:

Out of all the chemokines tested only TECK (Vicari, A.P., *et al., Immunity, 7(2)*:291-301 (1997)) acted as a chemoattractant for GPR-9-6/L1.2 transfectants, with 150 nM resulting in optimal chemotaxis. This falls into the range of 1nM-1μM for which other leukocyte chemokines are active. However, as we are using TECK that was generated by peptide synthesis,

A17

we cannot be sure that either post-translational modifications or further cleavage of TECK by factors outside the cell *in vivo* do not generate more active fragments, as is the case for CKB8 (Macphee, C.H., *et al.*, J. Immunol. 161:6273-6279 (1998)). TECK did not act as a chemoattractant for CCR1, CCR2, CCR4, CCR5, CCR6, CCR7, CCR9 and CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 L1.2 transfectants. However, some weak activity of TECK on CCR3/L1.2 transfectants which was approximately 20% of the chemotactic activity observed with eotaxin-1 was detected. This activity was blocked by anti-CCR3 mAbs, though TECK did not act as a chemoattractant for eosinophils. Therefore, TECK is probably not a physiological chemokine for the CCR3 receptor. This result is not unprecedented, as in previous studies MIP-1α has been shown to act as a chemoattractant for CCR4/HEK293 transfectants (Power, C.A., *et al., J. Biol. Chem., 270*:19495-19500 (1995)), but not CCR4/L1.2 transfectants (Imai, T.M., *et al., J. Biol. Chem., 272:*15036-15042 (1997)). In further experiments, only the T cell lines that express GPR-9-6 were found to chemotax to TECK, while among primary cells TECK was chemotactic for only a small subset of CD4 lymphocytes. Presumably, these cells represent the small subset of CD4 lymphocytes that express GPR-9-6, as the chemotaxis was blocked by anti-GPR-9-6 mAb 3C3. Additionally, only $\alpha 4\beta 7^{+ve}$ memory CD4 and CD8 lymphocytes chemotax to TECK, which would be the subset predicted to express GPR-9-6. TECK was originally described as a chemokine produced by thymic dendritic cell, whose expression is restricted to thymus and small intestine (Vicari, A.P., *et al., Immunity, 7(2)*:291-301 (1997)). Our Northern data confirms this observation and shows that the receptor for TECK, GPR-9-6, is also expressed at these sites. The expression of both chemokine receptor GPR-9-6 and its ligand TECK in small intestine and thymus predict a role for GPR-9-6 and TECK in T cell development and mucosal immunology.

A17 cont'd

Amendments to the specification are indicated in the attached "Marked Up Version of Amendments" (pages i-xi).